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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,571	10/11/2005	Barry Barton	PB60213	4768
20462 7590 12/26/2008 SMITHKLINE BEECHAM CORPORATION CORPORATE INTELLECTUAL PROPERTY-US, UW2220 P. O. BOX 1539 KING OF PRUSSIA, PA 19406-0939				
EXAMINER				
LONG, SCOTT				
ART UNIT		PAPER NUMBER		
1633				
NOTIFICATION DATE		DELIVERY MODE		
12/26/2008		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US\_cipkop@gsk.com

### Office Action Summary

**Application No.**

10/552,571

**Applicant(s)**

BARTON ET AL.

**Examiner**

SCOTT LONG

**Art Unit**

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 9/19/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 3-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-2 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 9/19/2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_
- Paper No(s)/Mail Date \_\_\_\_\_

### **DETAILED ACTION**

*The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 19 September 2008.*

#### ***Claim Status***

Claims 1-12 are pending. However, claims 3-12 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-2 are amended. Claims 1-2 are under current examination.

#### ***Priority***

This application claims benefit as a 371 of PCT/EP04/04001 (filed 04/13/2004) and from foreign application UNITED KINGDOM 0308696.4 (filed 04/15/2003). The instant application has been granted the benefit date, 15 April 2003, from foreign application UNITED KINGDOM 0308696.4.

#### ***Specification/ Drawings***

The examiner hereby withdraws the objection to the specification and drawings. The applicant has submitted amendments to overcome the objection based upon "sequences which represent polynucleotides for which no SEQ ID NO is been associated."

**RESPONSE TO ARGUMENTS**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. However, the examiner modifies his rejection to a Scope of Enablement rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working

examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The applicant's arguments have been fully considered and are partially persuasive. The applicant has amended the claims so that the claimed mutant microorganisms contain disrupted or deleted 5S clavam biosynthesis gene such that clavulanic acid production is at least maintained "when compared to the parent strain which has not had such disruptions."

In addition, the applicant has presented several arguments:

The applicant pointed out that the examiner has confused the various names of the paralogous genes, presented by the applicant and the cited art. The examiner apologizes for this confusion. Accordingly, the examiner hereby withdraws the portion of the rejection based upon the examiner's misunderstanding regarding the differences between the double mutant OAT1/OAT2 *S. clavuligerus* of Tahlan et al. and the instantly claimed SEQ ID NO:1/SEQ ID NO:5 double mutant *S. clavuligerus*.

The applicant also persuasively argues that the same trends of clavulanic acid production are found in different media for the various mutants. This part of the examiner's argument is withdrawn.

The examiner elaborates the scope of enablement below:

In the instant case, claims 1-2 while being enabled for a *S. clavuligerus* microorganism comprising DNA corresponding to one or more open reading frames

essential for 5S clavam biosynthesis, wherein said open reading frames are disrupted or deleted such that the production of 5S clavams by said *S. clavuligerus* is reduced and clavulanic acid production is at least maintained when compared with a *S. clavuligerus* parent strain, which has not had the relevant open reading frames disrupted or deleted, wherein the open reading frames are selected from: a) SEQ ID NO:1; and b) SEQ ID NO:1 and SEQ ID NO:5, does not reasonably provide enablement for the genus of claimed mutant *S. clavuligerus* microorganisms having (1) a disrupted or deleted *cvm6para* open reading frame, or (2) both a disrupted/deleted *cvm6* open reading frame and a disrupted/deleted *cvm6para* open reading frame. Basically, the specification only supports a single embodiment of a *S. clavuligerus* microorganism comprising a disrupted *cvm6para*, namely the microorganism having a disrupted SEQ ID NO:1 found in Example 5. Since the gene name, *cvm6para*, could encompass many alternatives other than SEQ ID NO:1, and the specification provides no support for other versions of this gene, the applicant is limited to the embodiment having a disrupted or deleted SEQ ID NO:1. Furthermore, a double mutant *S. clavuligerus* microorganism having a disrupted/deleted *cvm6* and a disrupted *cvm6para* is broader than the double mutant microorganism having a disrupted/deleted SEQ ID NO:1 and SEQ ID NO:5. Essentially this rejection can be overcome by more explicitly indicating the structure of the disruption or deletion found in the *S. clavuligerus* microorganism. Both claims 1 and 2 contain generic expressions of gene names, such as *cvm6para*, *cvm4*, etc., which do not accurately capture the structure of the mutant *S. clavuligerus* microorganism having

a disrupted or deleted SEQ ID NO:1, for example. Particularly, claim 1-c, 1-d, 2-a, and 2-b contain these problems.

Despite withdrawing portions of the pending rejection, there remains a problem regarding claims containing generic gene names, *cvm6* and *cvm6para*. The specification makes a link between *cvm6para* and SEQ ID NO:1, but does not explicitly limit the *cvm6para* gene to merely SEQ ID NO:1. Furthermore, the specification seems to sometimes refer to *cvm6para* as *cvm6par*. Without a clear identification of the sequence (i.e., SEQ ID NO) which is disrupted or deleted, a skilled artisan would not know how to make a *S. clavuligerus* having a disrupted or deleted open reading frame *cvm6para* (or *cvm6para* and *cvm6*). Therefore, the instant claims must recite the specific sequences that need to be disrupted or deleted as SEQ ID NOs.

The specification provides the following definitions: "Reduced" as used herein means that the levels of 5S *clavam* produced by the microorganism of the invention are lower than the levels produced in the corresponding *S. clavuligerus* strain which has not had the relevant open reading frames disrupted or deleted" (page 3, lines 18-20) and "at least maintained" as used herein means that the level of clavulanic acid produced in the microorganism of the invention is the same or greater than that produced in the corresponding *S. clavuligerus* strain which has not had the relevant open reading frames disrupted or deleted. " (page 3, lines 24-27). The specification also indicates that "the corresponding *S. clavuligerus* is therefore the 'parent' strain into which the disrupted or deleted open reading frames were subsequently introduced to generate

the microorganism of the invention." (page 3, lines 20-23, 27-29). The specification also teaches "'Disrupted' as used herein means that the activity of the gene (with regard to 5S clavam production) has been reduced or eliminated by, for example, insertional inactivation...or other mutagenesis techniques" (page 3, lines 3-9). The specification also teaches "'Deleted' as used herein means that the gene, or a segment thereof has been deleted (removed) from a larger polynucleotide" (page 3, lines 10-11). The specification is very clear about the meaning of these terms that are recited in the instant claims.

In conclusion, the examiner concludes that a skilled artisan would be enabled to make: a *S. clavuligerus* microorganism comprising a disrupted or deleted open reading frame selected from the group consisting of a) SEQ ID NO:1; and b) SEQ ID NO:1 and SEQ ID NO:5, wherein there is no or reduced activity from the genes encoded by said disrupted or deleted open reading frame, and wherein the production of 5S clavams by said *S. clavuligerus* is reduced and clavulanic acid production is at least maintained when compared with a *S. clavuligerus* parent strain. However, the examiner concludes that a skilled artisan would not be enabled to make the broader genus of *S. clavuligerus* having disrupted or deleted *cvm6* para. Likewise, to be enabled, *S. clavuligerus* comprising double mutations as recited in the pending claims would require explicit recitation of the embodiment encompassed by the SEQ ID NOs provided by the instant specification.

Therefore, the examiner hereby maintains the rejection of claims 1-2 under 35 USC 112, 1<sup>st</sup> paragraph (scope of enablement).



***NEW GROUNDS OF REJECTION***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "relevant" in claims 1-2 is a relative term which renders the claim indefinite. The term "relevant" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

No claims are allowed.

***Examiner Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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